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(54) Title: A METHOD OF ADMINISTERING LIPOSOMAL ENCAPSULATED TAXANE

(57) Abstract: The present invention provides a method for administering paclitaxel to human patients in which the occurrence and severity of adverse reactions such as neuropathy and alopecia, is greatly reduced over that of currently approved methods. Surprisingly, the method involves administering more paclitaxel to human patients over a shorter period of time than in previously known and approved methods.

A METHOD OF ADMINISTERING LIPOSOMAL ENCAPSULATED TAXANE

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a method for reducing the incidence of adverse reactions in human patients undergoing paclitaxel treatment.

BACKGROUND OF THE INVENTION

The use of taxanes, such as paclitaxel, as anti-tumor agents for patients suffering from diseases such as ovarian and breast cancer, is known. In addition, paclitaxel has been shown to be clinically potent as a synergistic agent when used in conjunction with other chemotherapy and radiation treatment. Paclitaxel has a unique mechanism of action and a broad spectrum of anticancer activity because paclitaxel shows stabilization of microtubules rather than disassembly of microtubules.

However, paclitaxel has extremely low solubility in water, which makes it difficult to provide a suitable dosage form. Currently, paclitaxel is prepared and administered in a vehicle containing Cremophor EL (a polyethoxylated castor oil) and ethanol in a 50:50 (vol/vol) ratio. This solution is diluted 1:10 in saline before being administered to humans. The stability of paclitaxel once diluted in saline solution is quite low. The drug degrades within 24 hours and, thus, handling of dosage for the patients becomes very difficult. Since, the drug precipitates from dilution, an on-line filter is utilized for the infusion of the drug to the patients.

As with most chemotherapeutic agents, conventional paclitaxel therapy is accompanied by a variety of undesirable side effects that cause discomfort and that can be life threatening. For example, alopecia (hair loss) occurs in 87% of all patients studied and nausea/vomiting occurs in 52% of patients. See Physicians Desk Reference, 54th Ed. Taxol® treatment is also frequently accompanied by neuropathy. The Physicians Desk Reference, 54th edition, indicates that 60% of treated patients experience peripheral neuropathy. In addition, 60% of treated patients experience myalgia and/or arthralgia. Among other listed toxicities are neutropenia (in 90% of patients), leukopenia (in 90% of patients), anemia (in 78% of patients), bleeding (in 25% of patients), thrombocytopenia (in 20% of patients), infections (in 14% of patients), and hypersensitivity reactions (in 41% of patients).

Although the hair loss associated with Taxol® treatment is not life threatening, it is typically viewed by both male and female patients as a sign of rapid progress of disease and produces anxiety and a loss of self-esteem in cancer

patients. Clearly, the reduction or prevention of alopecia would increase the quality of life and outlook of a cancer patient during treatment. The reduction of other toxicities, such as neuropathy, would also provide an immediate benefit to cancer patients.

Strategies for reducing paclitaxel toxicity, have included pretreatment of patients with antihistamine and corticosteroids, and by prolonging the infusion time from six to twenty four hours. U.S. Patent No. 5,621,001 (Canetta et al.) discloses a prolonged infusion time in a method for reducing peripheral neuropathy symptoms while maintaining an anti-tumor effect in patients suffering from ovarian cancer and undergoing paclitaxel therapy. This method involves reducing the amount of paclitaxel administered in a treatment from 175 mg/m^2 to about 135 mg/m^2 and increasing the administration time to about 24 hours. The administration of paclitaxel is repeated at least once, about 21 days after the preceding administration.

U.S. Patent No. 5,665,761 (Canetta et al.) discloses a pretreatment stage before administration of paclitaxel. The '761 patent provides for paclitaxel infusions over a duration of less than six hours, preferably about three hours, utilizing dosages of between about 135 mg/m^2 and about 275 mg/m^2, preferably between about 135 mg/m^2 and about 175 mg/m^2, after patients had been pretreated to alleviate or minimize hypersensitivity responses. For example, the patients were pre-medicated with steroids, antihistamines, and H_2-antagonists sufficient to at least prevent an anaphylactoid shock capable of causing acute hypersensitivity reactions and patient death. U.S. Patent No. 5,670,537 (Canetta et al.) also discloses this method of administration for a patient suffering from a paclitaxel-sensitive tumor, such as an ovarian tumor.

U.S. Patent No. 5,641,803, discloses the administration of paclitaxel to a patient, wherein about 135-175 mg/m^2 of paclitaxel is administered over a period of about three hours. Such a period purportedly was used to overcome, in part, some of the aforementioned problems associated with shorter infusion times, such as one hour, which had been employed with the conventional paclitaxel formulations containing polyethoxylated castor oil.

In yet another attempt to address the toxicity concerns of the conventional paclitaxel formulation, U.S. Patent No. 5,696,153 suggests the use of an administration regimen wherein lower amounts of paclitaxel of from 45 to 120 mg/m^2 is administered over a period of 60 to 180 minutes, a plurality of times during a 21 day period, with each infusion being separated by an interval of between 4 to 5 days.

However, even with prolonged infusion times and pretreatments with antihistamines and corticosteroids, patients suffer from toxicities, such as alopecia, neuropathy, and other toxicities, some of which are life threatening. Therefore, new drug delivery systems are needed that can enhance the efficacy and/or reduce systemic toxicity.

U.S. Patent No. 5,648,090 (Rahman et al.) and U.S. Patent No. 5,424,073 (Rahman et al.) provide a liposomal encapsulated paclitaxel, or antineoplastic derivative, which is used to treat cancer in mammals. The '090 and '073 patents disclose a method of modulating multidrug resistance in cancer cells in a mammalian host by administering to the host a pharmaceutical composition of a therapeutically effective number of liposomes that contain cardiolipin and a taxane in a pharmaceutically acceptable excipient. Methods for using those compositions in humans in a manner that reduces toxicity, such as alopecia, neuropathy, nausea are not disclosed.

Currently, the only methods known for reducing the toxicity of paclitaxel treatment in humans is to reduce the amount and/or rate of the drug administered to patients. The only approved protocol for administering paclitaxel is that for Taxol® in the New Drug Application ("NDA")owned by Bristol-Myers Squibb. This protocol is limited to Taxol® dosages of no more than 175 mg/m^2 and administration times of no less than three hours. In addition, all patients are premedicated with corticosteroids, diphenhydramine and H_2 antagonists. Even under these conditions, in addition to other adverse reactions, it is reported that approximately 60-70% of patients experience neuropathy and 87% experience alopecia. Consequently, there remains a need for a method of administering larger quantities of taxane in a shorter period of time which is accompanied by less frequent and less severe adverse reactions. Such methods would improve the efficacy of taxane therapy and alleviate the discomfort and complications that restrict current taxane administration methods. The present invention provides such a method.

SUMMARY OF THE INVENTION

The present invention provides a method for reducing adverse reactions such as neuropathy and alopecia, in human patients undergoing paclitaxel treatment. The method involves administering high concentrations of paclitaxel to patients over a period of about one hour or less. Concentrations of about 90, 135, 175 , 250, and up to about 300 mg/m^2 of paclitaxel are administered to patients within one hour. Surprisingly, the occurrence of adverse reactions like alopecia

and neuropathy, including peripheral neuropathy, are reduced as compared to the frequency and severity of adverse reactions reported for the administration of Taxol® described previously. Paclitaxel is administered to patients in a liposomal formulation containing cardiolipin, cholesterol, α-tocopherol and the liposome-forming material, phosphatidylcholine. The formulation can be prepared as described below in Example 1. The present method also contemplates optional patient premedication as described in Example 3.

The present invention provides a method of administering relatively high concentrations of taxane to human patients over a short period of time. For example, taxane can be administered to humans in less than an hour in an amount from about 75 to 300 mg/m^2. Unique liposomal formulations of paclitaxel or its antineoplastic derivatives facilitate such treatments. The method does not require premedication, as with anti-hypersensitivity agents. As a result, the present invention provides an improved method for treating cancer with taxane.

These and other advantages of the present invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.

The invention may best be understood with reference to the following detailed description of the preferred embodiments.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a method of administering a taxane to a patient, especially a human patient, in need of treatment with a taxane. In part, the present invention provides a delivery system for a taxane to a host which is characterized by the avoidance of taxane solubility problems; improved taxane stability; the avoidance of anaphylactic reactions, cardiotoxicity, alopecia, neuropathy; the ability to administer a taxane as a bolus or short infusion, rather than an extended infusion of free taxane; the increased therapeutic efficacy of taxane; and the modulation of multidrug resistance in cancer cells.

The taxane or antineoplastic derivative thereof, is delivered in a liposomal formulation. Any suitable taxane or derivative can be used in the present method. Suitable taxanes when used in accordance with the disclosed methods provide the aforementioned benefits. Preferably, the taxane is paclitaxel. A suitable derivative of paclitaxel is taxasm. Other suitable taxanes are 7-epipaclitaxel, t-acetyl paclitaxel, 10-desacetyl-paclitaxel, 10-desacetyl-7-epipaclitaxel, 7-

xylosylpaclitaxel, 10-desacetyl-7-glutarylpaclitaxel, 7-N,N-dimethylglycylpaclitaxel, 7-L-alanylpaclitaxel, taxotere, and mixtures thereof.

The pharmaceutical composition may also include a suitable cardiolipin. Suitable cardiolipin may be from either a natural or synthetic source. The taxane, such as paclitaxel, is encapsulated in liposomes using the cardiolipin. In addition to cardiolipin, the taxane may be encapsulated in liposomes with phosphatidylcholine and cholesterol. Such lipid compositions provide over 90% encapsulation of the drug in liposomes.

The liposomal encapsulated taxane can be prepared by any suitable process. For example, the taxane or a derivative thereof can be dissolved in a suitable solvent. Generally, suitable solvents are non-polar or slightly polar and can be evaporated without leaving toxic residue behind. Suitable solvents include such diverse solvents as ethanol, methanol, chloroform, butanol or acetone. Cardiolipin can also be dissolved in a suitable solvent as described for taxane and the taxane and the cardiolipin solutions can be mixed. The remaining lipophilic material can be dissolved in a suitable solvent, which may be the same as or different from the taxane containing solvent. The solvent will have low polarity such as chloroform, butanol or a non-polar solvent, such as n-hexane. The solvent mixture containing the taxane and cardiolipin can be mixed with the solution containing the remaining lipophilic components.

The solvent is removed, from the mixture by a suitable method such as by lyophilization to produce a dry lipid film that contains the drug. The mixture is stored in this form, optionally under an inert gas atmosphere, such as an N_2 atmosphere. The dry lipid film can be stored at low temperatures, such as –20° C for extended periods of time until liposomes are hydrated and prior to use.

Liposomes can be formed by adding any suitable solution to the lipid film. Typically, suitable solutions are polar solutions, preferably, aqueous saline solutions. Once the solution is added, liposomes can be formed by mixing, for example, as by vortexing. Where smaller vesicles, such as unilamellar vesicles, are desirable the solution can be sonicated. In certain methods, suitable preparations can be mixtures of multilamellar vesicles and unilamellar vesicles.

The liposome is a closed structure composed of lipid bilayers surrounding an internal aqueous space. Generally, the liposomes may be neutral, negative or positively charged. Cationic liposomes can be formed from a solution containing phosphatidyl choline, cholesterol, and stearyl amine. Anionic liposomes can be formed, for example, from solutions containing phosphatidyl choline, cholesterol, and phosphatidyl serine or more preferably, cardiolipin. Other additives can also

be included in the liposomes to modify the properties of the resulting preparations. For example, preferred preparations also include α-tocopherol.

Storage conditions can vary. Preferably, mixtures of lipophilic components are stored as dry lipid films at about -20° C. Once hydrated, liposome suspensions of the pharmaceutical composition can be stored and are stable in buffered or unbuffered saline solutions for periods of hours to months, depending upon the temperature, paclitaxel content, and phospholipid constituents.

The liposomal drug delivery system which features a high drug to carrier ratio can alter drug pharmacokinetics, maintaining the plasma concentration of the drug at an increased level over a longer period of time. The biodegradability and the low inherent toxicity and immunogenicity of liposomal preparations reduces toxicity with respect to free-floating taxanes in the plasma.

The present liposomal formulations provide a drug-delivery system which allows infusion of high concentrations of taxane in a relatively stable form and which provides sustained therapeutic benefits at target sites, while maintaining low concentrations of insoluble free taxane and minimal adverse toxic effects than were previously known. For example, infusion of encapsulated paclitaxel provides higher peak plasma concentrations, longer presence of the drug in the body, and higher AUC ("area under the curve" measurement of plasma concentration over time) than the conventional paclitaxel.

The present pharmaceutical composition can be administered in amounts of at least 50 to 300 mg of active compound/m^2 of patient surface area, within a period of about one hour or 45 minutes such that adverse reactions are reduced in patients. Longer administration times may be used but this is not preferred. For example, in a 70 kg human, about 0.5 to 5.0 mg active compound per kg of body weight can be safely administered in about 45 minutes. Preferably, about 1.0-3.0 mg of active compound per kg of body weight is administered. Alternatively, amounts of 75, 135, 175, 250, and 300 mg/m^2 can be administered.

Liposomal encapsulated taxane has a substantial beneficial effect in overcoming multidrug resistance in cancer cells which are subjected to chemotherapy. By using the liposomal composition of the present invention, it is possible to reduce the tendency of cancer cells subjected to chemotherapy to develop resistance to the chemotherapeutic agents used for chemotherapy such as anthracycline glycosides. This method includes administering to a host a pharmaceutical composition of a liposomal encapsulated taxane of the present invention in accordance with the administration protocol.

Taxanes and the anti-neoplastic derivatives thereof may be used to treat any disease that is susceptible to treatment. Such compounds are thought to function by promoting the assembly of microtubules or prohibiting the tubulin disassembly process. These compounds are particularly advantageous in the treatment of taxane sensitive diseases such as mammalian lymphoma, ovarian, breast, lung and colon cancer, and particularly those conditions in humans.

The present liposome compositions can be administered intravenously, intraperitoneally, to an isolated portion of a mammalian body, particularly a human body, such as an arm or leg, or in the case of a human, a hand, or can be injected directly into a tumor.

The following examples further illustrate the present invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

Paclitaxel can be encapsulated in liposomes of cardiolipin, phosphatidylcholine, cholesterol and α-tocopherol. The composition described in this example, provides for over 90% encapsulation of the drug in liposomes. The paclitaxel in liposomal formulation is stable for days at room temperature and at -20° C for at least 5 months. No degradation or precipitation of paclitaxel is observed at any storage temperature and the preparation appears to be ideally suited for systemic administration in accordance with the present invention.

The proportion of lipids per mg of paclitaxel is:

1.8 mg cardiolipin
9.0 mg phophatidylcholine
3.0 mg cholesterol
0.1 mg α-tocopherol

The liposome encapsulated paclitaxel can be manufactured using the following procedure.

8.89 kilograms of t-butyl alcohol are added to a 12.0 liter flask and heated to 40-45° C. The following additions are made sequentially with mixing until dissolution and heating at 40-45° C: 3.412 grams of D-α-tocopherol acid succinate, 205 grams of egg phosphatidylcholine, 22.78 grams of paclitaxel, 41.00 grams of tetramyristoyl cardiolipin, 68.33 grams of cholesterol.

The resulting solution is filtered through a 0.22 micron filter and filled into sterile vials, each containing about 10.1 grams of filtrate. The vials are stoppered and subjected to lyophilization. They can be stored at –20° C until use.

Liposomes are prepared from the dry lipid film, as needed, with 25 ml of normal saline solution. The mixture is allowed to hydrate at room temperature for about one hour, after which time the vials are vortexed for about one minute and sonicated for about 10 minutes in a bath type sonicator at maximum frequency. An appropriate amount of the contents of the vial can be transferred to an infusion bag and infused into a patient in accordance with the present invention.

EXAMPLE 2

The following study demonstrates that a large quantity of taxane can be rapidly administered to humans without inducing a substantial toxic reaction. Both hematological toxicity and nonhematological toxicity were evaluated. In addition, the study was used to determine in human patients the dose-limiting toxicity, the maximum tolerated dose and the untolerated dose for the liposomal formulation described in Example 1.

Vials containing liposomal paclitaxel were prepared as in Example 1. The preparations were 1 mg/ml paclitaxel in liposomes. The contents of the vials were transferred to infusion bags at the appropriate dosages and administered to patients over about a 45 minute period.

Patients selected for the study had a measurable or evaluable metastatic or locally recurrent malignancy and had no significant hope of cure or palliation by other conventional therapies. In addition, they had no evidence of spinal cord compression or carcinomatous meningitis. Patients had not undergone chemotherapy or radiotherapy within the four weeks prior to treatment. Those patients that had undergone prior chemotherapy or radiotherapy exhibited complete hematologic recovery prior to treatment in this study. All patients had an ECOG (Eastern Cooperative Oncology Group) performance status of 0 or 1 and had a life expectancy of at least 3 months. Patients in the study were all over the age of 18, were free of infection and had recovered from the effects of any major surgery which must have occurred more than three weeks prior to entering the study. Within the immediate two weeks prior to the instant tests all patients had a white blood cell count of over $3000/mm^3$, a platelet count of over $100,000/mm^3$, serum creatinine of less than 1.8 mg/dl or creatinine clearance of more than 60/cc/min and serum bilirubin of less than 1.5 mg/dl.

Treatments were administered intravenously over about a 45 minute period. At least three patients were treated at each dosage level. Dosages were about 90 mg/m^2, 135 mg/m^2, 175 mg/m^2, 250 mg/m^2, and 300 mg/m^2 allowing for normal laboratory and therapeutic dose variation. The formulation was given as a single

agent without pretreatment with steroids, antihistamines or other therapeutic agents such as anaphylaxis inhibitors. Where the treating physician considered it appropriate, treatments were repeated every 21 days. Each patient was subjected to a single treatment regimen.

Hematologic and nonhematological toxicities were evaluated in patients by the evaluation of blood specimens in accordance with methods well known in the medical arts. Drug efficacy was also evaluated. The results of this study are shown in Table I below.

Common toxicity grades established by the National Cancer Institute were employed to determine drug toxicity. Dose-limiting toxicity is defined as any grade 3 or higher non-hematologic toxicity for 7 or more days occurring during cycle 1 of chemotherapy. An untolerable dose is defined as the dose level at which at least 1/3 to 2/3 of the patients have dose-limiting toxicity. The maximum tolerated dose level is defined as the dose level at which 0/6 or 1/6 patients experience dose-limiting toxicity and at least 2/3 or 4/6 patients treated at the next higher dose level experience dose-limiting toxicity.

This study demonstrated that a large quantity of taxane could be administered to a human without inducing a substantial hematological or nonhematological toxic reaction. Nonhematological toxicity was generally minor but became more pronounced at the highest dosage level. Similarly, hematological toxicity was mild but became more pronounced at the highest dosage. At least 300 mg/m^2 of taxane could be administered to a human patient in a 45 minute period without inducing very substantial hematological toxicity. The dose limiting toxicity was about 300 mg/m^2 when drug was administered in a 45 minute period. The untolerable and maximum tolerable doses were not yet determinable from this study but were at least 250 mg/m^2. With one exception, the cancer had not progressed or was improved in each of the patients studied.

TABLE 1

Patient Number	Treatment Cycles	Dose (mg/m^2)	Heme Toxicity[1]	Nonhematological Toxicity	Best Response	Off study due to
001	2	90	None	HSR[2]		P.D.[3]
002	11+	90	Mild		Stable	
003	6	90	Mild	(Seizure)	Stable	P.D.
004	2	135		HSR		P.D.
005	6	135	Mild	Muscular & hepatic	Stable	elective
006	8+	135	Mild	(HA, fever, pharyngitis, wheezing)	Progressed	
007	3	175	Mild	(diarrhea)		P.D.
008	2	175	Mild	Mild hepatic		P.D.
009	1	175	Mild	Recurrent HSR; Nausea/fatigue; Mild hepatic		HSR
010	2	250	Mod	(hemoptysis)		P.D.
011	4+	250	Mild	Mild hepatic (HA, diarrhea, chills & sweats) Esophagitis grade3 after cycle 3	Stable	
012	3	250	Mild	Mild hepatic		P.D.
013	2+	250	Mild	Mild GI, HSR		
014	2+	300	Mod	Hepatic, Esophagitis grade 3	Improved	
015	1+	300	Severe	Mild HSR, Hepatic		
016	1+	300	Severe	Esophagitis grade 3		

[1] neutropenia, anemia, thrombopenia
[2] hypersensitivity reaction: flushing, back pain, pruritis
[3] physician or patient discretion

EXAMPLE 3

The data reported in Example 3 demonstrates that the methods of the present invention can be used to treat patients with higher concentrations of paclitaxel and with reduced adverse reactions, especially including reduced neuropathy and alopecia as compared to the incidence reported for Taxol® in the Physicians Desk Reference, 54th Edition and U.S. Patent No. 5,621,001 (Caretta et al.). The present example incorporates data from Example 2 above along with data from the study of 10 additional patients and observations after further treatments of patients 2, 5, 6, 13, and 15 over that reported in Example 2. Adverse drug reactions were determined using standard medical procedures. All observations are reported in Tables 2-4 below which provide cumulative results for all 26 patients. Patients were evaluated for the adverse reactions listed below and neuropathy, which has not yet been observed in any patient treated in these studies. Patients 1-19 were not premedicated while patients 20-26 were premedicated with diphenhydramine 25/50 mg and hydrocortisone (100 mg) using standard procedures.

TABLE 2

Patient Number	Age/Sex	Cancer Type	Treatment Cycles	Dose (mg/m^2)	Best Response
001	63/F	NSCLC[1]	2	90	Progression
002	68/M	NSCLC	20+	90	Stable
003	60/M	NSCLC	6	90	Progression
004	54/M	NSCLC	2	135	Progression
005	71/F	NSCLC	6	135	Stable
006	64/F	NSCLC	17+	135	Minor Response
007	76/F	NSCLC	3	175	Progression
008	57/M	NSCLC	2	175	Progression
009	61/F	NSCLC	1	175	None
010	69/F	SCLC[2]	2	250	Progression
011	44/F	NSCLC	4	250	Stable
012	51/M	NSCLC	3	250	Progression
013	53/M	NSCLC	4	250	Stable
014	38/F	NSCLC	2	300	Progression
015	44/F	Breast	5	300	Minor Response
016	72/F	NSCLC	3	300	Partial Response

(Table 2-continued)

017	77/M	NSCLC	2	250	Progression
018	39/M	NSCLC	1	250	Progression
019	66/M	NSCLC	2	175	Progression
020	40/M	NSCLC	5+	175	Stable
021	46/F	nasopharyngeal	3	175	Stable
22	67/F	breast	3+	175	Partial Response
23	60/M	NSCLC	2	175	Progression
24	58/M	unknown	2+	175	
25	58/F	NSCLC	1+	175	
26	51/F	NSCLC	1+	175	

+ Patients continuing on study
[1] NSCLC is non-small cell lung cancer
[2] SCLC is small cell lung cancer

Table 2 provides an indication of the efficacy of the present method against various types of cancer. A partial response was observed in two patients, one having breast cancer and another having non-small cell lung cancer. The breast cancer patient received a 175 mg/m^2 dose and the lung cancer patient received a dose of 300 mg/m^2. A minor response was observed in another non-small cell lung cancer patient at 135 mg/m^2 and a breast cancer patient who received 300 mg/m^2 of paclitaxel. In six additional patients the disease was stabilized by the present methods. Stabilization was observed in one patient suffering from nasopharyngeal cancer after treatment with a dose of 175 mg/m^2 paclitaxel. Five patients suffering from non-small cell lung cancer were stabilized by the present treatment at doses of 90 (1 patient of 3), 135 (1 patient of 3), 175 (2 patients of 8 evaluated), and 250 mg/m^2 (2 patients of 6).

One aspect of the present invention is the reduction in hematologic toxicity associated with the present paclitaxel treatment. Patient blood samples were analyzed as described in Example 2 for white blood cell count (WBC), absolute neutrophil count (ANC), platelet counts (Plt), and hemoglobin concentration and World Health Organization grades were assigned to patients. Table 3 provides a summary of hematologic toxicity. As shown in Table 3, dose dependent neutropenia was the most significant adverse reaction observed in the present study at dosages of 250 and 300 mg/m^2. At a dosage of 250 mg/m^2 one patient experienced grade 4 neutropenia leading to sepsis and death. Significant instances of

leukopenia were also observed at the higher dosages. The incidence of thrombocytopenia and anemia was lower and less severe.

TABLE 3

LEP mg/m^2	No. Patients	ANC Grade 3/4	WBC Grade 3/4	HgB Grade 2/3	Plt Grade 2/3
90	3	0/0	0/0	0/0	0/0
135	3	0/0	0/0	2/0	0/0
175	11	0/3	3/0	2/0	1/0
250	6	2/2	1/0	2/0	1/0
300	3	0/3	1/2	0/2	1/1

The incidence and spectrum of nonhemotologic toxicity is summarized in Table 4. Surprisingly, Table 4 shows that no alopecia was observed in patients treated with either 90, 135, and 175 mg/m^2 of paclitaxel. At a dosage of 250 mg/m^2 paclitaxel only one case of grade 2 alopecia was observed out of a total of 6 patients. Similarly, the incidence and severity of alopecia at the highest dose of 300 mg/m^2 was remarkably low. Out of three patients at this dosage level, only one exhibited grade 2 alopecia and one patient exhibited grade 1 alopecia. Overall the incidence and severity of alopecia is profoundly reduced from the levels associated with Taxol® treatment by known and approved methods.

TABLE 4

LEP mg/m^2	No. Patients	Incidence	Grade	Toxicity
90 & 135	6	1	1	diarrhea
175	11	1	3	neutropenic fever
	11	1	2	mucositis
	11	3	1	diarrhea & fatigue
250	6	1:1	4	bronchospasm:neutropenic fever
	6	1	3	mucositis
	6	1:1:1	2	fatigue:N/V:alopecia
300	3	2	3/4	mucositis
	3	1:1:1	3	diarrhea:N/V:neutropenic fever
	3	1:1	2	alopecia:fatigue
	3	1	1	alopecia

Quite surprisingly, no neurological toxicity was observed when paclitaxel was administered by the present methods, at any dose level. More specifically, none of the patients treated in this study appeared to exhibit peripheral neuropathy, arthralgia, or myalgia. This observation is

quite remarkable given the short administration times of approximately 45 minutes and the high concentrations of up to 300 mg/m^2 paclitaxel. The incidence of neuropathy observed in the present study is a particularly surprising and profound reduction from the 60 to 70% incidence reported for prior Taxol® treatment methods.

At a dosage of 250 mg/m^2 one patient experienced grade 4 bronchospasm. At 300 mg/m^2 one patient experienced a grade 3/4 mucositis which led to sepsis and death after each of three cycles of therapy in which the doses were reduced from 300 to 250 to 175 mg/m^2. Another patient experienced grade 3 mucositis at this dose level.

In the group of patients that were not premedicated 6 exhibited some form of infusion toxicity. Of this group 3 patients exhibited moderate flushing and severe back pain, 1 patient exhibited moderate flushing and back pain, 1 patient exhibited mild flushing, and 1 patient exhibited moderate rigors.

All of the references cited herein, including patents, patent applications, and publications, are hereby incorporated in their entireties by reference.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred embodiments may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

WE CLAIM:

1. A method for reducing neuropathy in a human patient undergoing paclitaxel treatment comprising administering to said patient from about 135 to about 300 mg/m^2 of paclitaxel in a liposomal formulation over a period of about one hour.

2. A method for reducing peripheral neuropathy in a human patient undergoing paclitaxel treatment comprising administering to said patient from about 135 to about 300 mg/m^2 of paclitaxel in a liposomal formulation over a period of about one hour.

3. A method for reducing alopecia in a human patient undergoing paclitaxel treatment comprising administering to said patient from about 135 to about 250 mg/m^2 of paclitaxel in a liposomal formulation over a period of about one hour.

4. A method for reducing alopecia and neuropathy in a human patient undergoing paclitaxel treatment comprising administering to said patient from about 135 to about 250 mg/m^2 of paclitaxel in a liposomal formulation over a period of about one hour.

5. A method for reducing alopecia and neuropathy in a human patient undergoing paclitaxel treatment comprising administering to said patient from about 135 to about 250 mg/m^2 of paclitaxel in a liposomal formulation comprising a liposome-forming material, cardiolipin, and a pharmaceutically acceptable excipient.

6. A method as in any one of claims 1-5 wherein said patients are premedicated before administering said paclitaxel.

7. A method as in any one of claims 1 or 2 further comprising administering to said patient about 300 mg/m^2 of paclitaxel in a liposomal formulation.

8. A method as in any one of claims 1-6 further comprising administering to said patient about 250 mg/m^2 of paclitaxel in a liposomal formulation.

9. A method as in any one of claims 1-6 further comprising administering to said patient about 175 mg/m^2 of paclitaxel in a liposomal formulation.

10. A method as in any one of claims 1-6 further comprising administering to said patient about 135 mg/m^2 of paclitaxel in a liposomal formulation.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07619

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/335, 31/21
US CL : 514/449, 510

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/449, 510

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, CAPLUS, EMBASE,MEDLINE,BIOSIS
search terms: paclitaxel, taxol, liposome, liposomal, cardiolipin, alopecia, neuropathy, neuropathies

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93/18751 A1 (GEORGETOWN UNIVERSITY) 30 September 1993 (30.09.1993), see entire document.	1-10
A	US 5,994,409 A (STOGNIEW et al.) 30 November 1999 (30.11.1999).	1-10
A	US 5,919,816 A (HAUSHEER et al) 06 July 1999 (06.07.1999).	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 25 MAY 2000	Date of mailing of the international search report 12 JUN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JENNIFER KIM Telephone No. (703) 308-0196

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